Statistical Analysis Plan

Statins Evaluation in Coronary procedUres and REvascularization Trial (SECURE-PCI)

A MULTICENTER RANDOMIZED CLINICAL TRIAL TO EVALUATE THE EFFECT OF ATORVASTATIN IN PATIENTS WITH ACUTE CORONARY SYNDROME UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

Version 2.0, November 13th, 2017
Protocol version 6.0, August 22nd, 2017

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Summary

1. Study Overview

SECURE-PCI is a multicenter, pragmatic, randomized, double-blind, controlled trial, including patients with acute coronary syndrome (ACS) who intend to undergo percutaneous coronary intervention (PCI) in approximately 75 centers in Brazil. Patients will be randomized in a 1:1 ratio to receive atorvastatin 80mg (or matching placebo) one dose before and another dose 24 hours after PCI. Patients, health care providers, and outcomes adjudicators will be blinded to treatment assignment.

1.1 Eligibility

1.1.1 Inclusion criteria

Patients of both genders, aged ≥ 18 years, and with acute coronary syndrome intended to be treated with PCI during the same hospitalization (including those with ST segment elevation MI treated with primary angioplasty) will be included provided they present at least 2 of the following criteria.

- Angina-like chest pain or ischemic equivalent chest pain;
- Electrocardiographic abnormalities compatible with angina (ST segment elevation higher than 2mm on precordial leads and higher than 1mm on peripheral leads or new left bundle branch block, ST segment depression of at least 0.5 mm or T wave inversion greater than 0.2mV) on at least two contiguous leads;
- Values above the upper limit reference value for myocardial markers of necrosis (troponin and CK-MB).

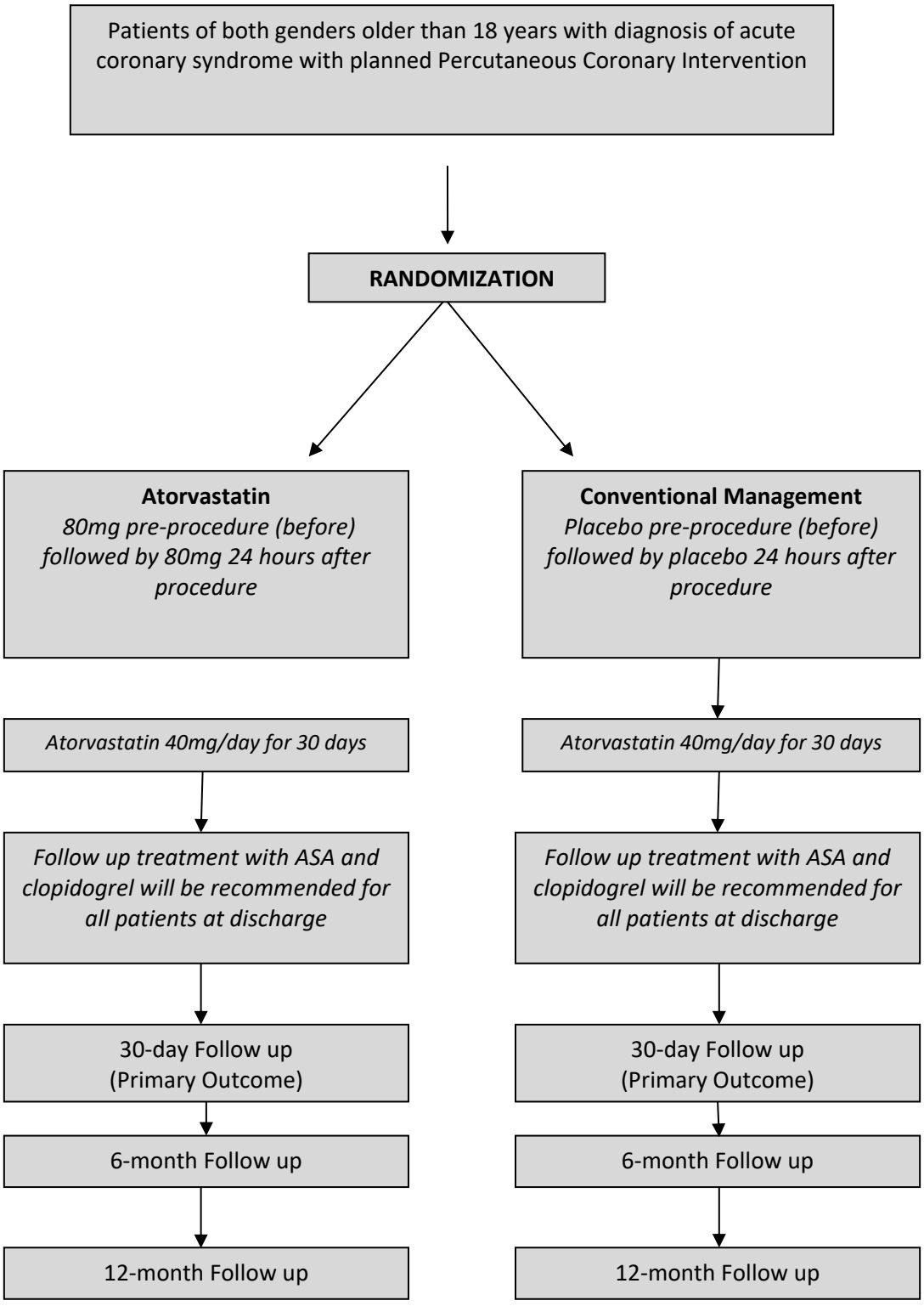
Previous use of statins (for any time prior to inclusion in this study) is not considered an exclusion criterion for the SECURE-PCI Trial. Therefore, both statin-naïve patients and previous statin users will be assessed. However, the patient should not have received a maximum dose of statin in the last 24 hours before the PCI to be eligible for the study, due to safety reason. Maximum dosage is considered as:

Atorvastatin 80 mg, Rosuvastatin 40 mg, Simvastatin 80mg, Pravastatin 40 mg, and Fluvastatin 80 mg. Differences in the effects of treatment between these two groups of patients will be assessed using pre-specified subgroup analyses.

1.1.2 Exclusion criteria

- Pregnant and breastfeeding women or women aged < 45 not using effective contraceptive methods (regular use of contraceptive pills, IUD, tubal ligation).
- Previous inclusion in the study
- Refusal to sign the written informed consent form (ICF).
- Concurrent participation in other RCTs involving the use of lipid lowering drugs.
- Drug hypersensitivity.
- History of advanced liver disease (primary biliary cirrhosis, sclerosing cholangitis, acute hepatitis, persistent elevation of liver transaminases > 3 times above the upper limit of normal).
- Use of any statin at a maximum dose in the last 24 hours before PCI.
- Use of any fibrate in the last 24 hours before the loading dose.

1.1 Flowchart



1.2 Concealed Randomization and Blinding

Patients will be randomized in a 1:1 ratio by a central web-based randomization system developed by the Research Institute HCor (São Paulo, Brazil) to ensure allocation concealment. Randomization will be stratified by center and by the presence or absence of the ST-elevation myocardial infarction with a plan to perform primary percutaneous coronary intervention.

The study drug, atorvastatin and placebo, will be identical, in terms of size, shape, and color. Thus, in the SECURE-PCI Trial, patients, investigators, and outcome assessors will be blinded for treatment allocation throughout the study period.

1.3 Study Drug

Patients presenting with ST-elevation myocardial infarction undergoing primary PCI will receive the study drug any time without delays before PCI. Those patients presenting with non-ST myocardial infarction or unstable angina will receive the study drug between 2 and 12 hours before PCI. All participants will receive a re-loading dose of atorvastatin 80 mg or matching placebo 24 hours after PCI.

Patients, from both groups, treatment and placebo, will receive a maintenance dose of atorvastatin 40mg, which should start one day after the re-loading dose and continued up to 30 days after PCI. Subsequently, prescription of statins will be according to the assisting physician discretion.

1.4 Outcomes

All outcomes will be assessed by an independent blinded Clinical Events Classification Committee. All events will be revised by at least two independent members of the committee.

1.4.1 Primary Outcome

The primary outcome of the SECURE-PCI Trial will be major adverse cardiovascular events (MACE), defined as a composite outcome of all-cause mortality (Cardiovascular, Non-cardiovascular, or Unknown), myocardial infarction (Peri-PCI, spontaneous and Peri-Coronary Artery Bypass Graft surgery), stroke or unplanned coronary revascularization until 30 days.

We will access the outcome considering time-to-event considering as time zero for each patient the randomizations date as usual.

1.4.2 Secondary Outcome

Secondary outcomes are:

- MACE until 12 months;
- Individual components of MACE until 12 months;
- Cardiovascular death until 12 months;
- New target vessel revascularization until 12 months;
- Stent thrombosis until 12 months;
- Bleeding and Rhabdomyolysis within 7 days or until hospital discharge.

All considerations about time-to-event calculations also apply to secondary outcomes, except bleeding that will be evaluated as a binary outcome only until 7 days.

2. Sample Size Determination

The sample size calculation was performed based on previous studies in the area[1] [2]. Considering a primary outcome (MACE) rate of 12.3% at 30 days, a relative risk reduction (RRR) of 25%, a power of 90% and a two-sided alpha of 5%, at least 4,192 patients should be included in the study. The expectation is that around 70% of the patients will undergo PCI, which will assure approximately 80% power for this pre-specified analysis.

3. Statistical Analysis Plan

Baseline characteristics, procedural characteristics, and laboratory results will be summarized for non-missing observation using relative and absolute frequencies, means and standard deviation (SD), or median and interquartile range (IQR), whenever appropriate as indicated in dummy table 1 to 5, which we intend to include in the main results paper.

All statistical analyses will be conducted according to intention-to-treat principle as the primary analysis. Thus, the patients will be analyzed according to the group to which they were allocated, Atorvastatin or Placebo, even if the adherence was not satisfactory, or if the patient decided to change medication along the follow up period, or if the loading dose was not administrated for any causes.

The hypothesis will be tested at the 5% two-sided significance level. No multiplicity adjustment will be made to p values and confidence intervals.

Statistical analysis will be conducted performed with the software R (R foundation for Statistical Computing, Vienna, Austria)[3] in their latest version.

3.1 Study Population

The expectation of the effect of the loading dose of Atorvastatin against Placebo based on previous studies is more robust in patients that underwent PCI[1]. For that reason, the PCI population was considered in the sample size calculation and all following analysis will be done both in the full sample and in the specific group of patients that actually underwent PCI. In both cases, intention-to-treat principle, as specified above, should be considered.

3.2 Timing of final analysis

Last patient was enrolled in the study in October 2017. It is expected that data base are cleaned a ready to analysis of primary endpoint in 30 days in December 2017.

3.3 Baseline and procedural characteristics comparisons

The baseline and procedural characteristics will be summarized by treatment group for the intention-to-treat as depicted in the tables 1 and 2.

3.4 Laboratory test levels

Laboratory measurements will be summarized at baseline and at 30 days. Serum creatinine levels will be reported post-PCI and change from pre-PCI (Table 3). We will use t test if the normality distribution assumption holds or Mann-Whitney test instead. The Gaussian distribution will be assessed by visual inspection and D'Agostino-Pearson normality test.

3.5 Primary outcome analysis

We will report the absolute and relative frequencies of MACE within 30 days after PCI (Table 4). In time-to-event (MACE) analysis in both arms will be assessed using Kaplan-Meier curves, and hazard ratio with 95% confidence interval will be calculated with Cox proportional hazards model with a factor treatment group. To secondary publication with 12 months follow up same models are expected to be use. Proportional hazard assumption will be checked by visual inspection and weighted residuals test[4].

3.6 Secondary outcome analysis

Every primary outcome component until 30 days will also be evaluated using Cox proportional hazard models. We will perform the same analysis for the time-to-occurrence of cardiovascular death, Peri-PCI MI and Other MI, target vessel revascularization and stent thrombosis.

We will assess the effect of the treatment on the incidence of bleeding and rhabdomyolysis within 7 days or until hospital discharge with risk ratios, 95% confidence intervals calculated with Wald's likelihood ratio approximated and chi-squared test.

Table 4 described a possible presentation of those results.

3.7 Sensitivity Analysis

We plan to evaluate the primary outcome in the following strata:

- Only patients that received the loading dose accordingly.
- Considering only events that happened before the administration of the loading dose.
- Restricted to the population that underwent PCI, considering only patients that have event after the procedure.

3.8 Subgroup Analyses

Treatment effect on 30-day MACE will be analyzed in the following subgroups:

- Males vs. Females
- Age (65 ≤ vs. > 65)
- Patients with ST-elevation myocardial infarction vs. patients with non ST-elevation MI vs. patients with unstable angina.
- Patients with previous statin use vs. patients without previous statin use (> 30 days)
- Patients with pharmacological stents vs. patients with conventional stents.

Effects on subgroups will be analyzed by interaction parameter between subgroup and the studies groups by Cox proportional hazard models. Forest plots will be generated for the subgroup analyses as in Table 5.

3.9 Missing data

Outcomes are defined as time to event in will be analyzed with survival models considering the patient censured at the last realized visit. If the patient only has information available until hospital discharge, it will be considered censured at this time point.

We are aware of few missing dates and information of PCI procedures, we will treat specific procedure characteristics as missing when reporting those data, except for the date and hour for the PCI, which will be imputed equal to the angiography date and hour.

We did not intend to impute any further value; however, if other post-hoc analysis requesting covariates that are not completed, we shawl impute those values considering multiple imputation technics from R package *mice* to estimate possible missing covariates data[5].

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236 ## Tables

237 **Table 1:** Baseline Characteristics of the Patients.

Characteristic	Atorvastatin (n = xxxx)	Placebo (n = xxxx)
Age (years) – mean ± sd	xx.x ± xx.x	xx.x ± xx.x
Female sex – n/total no. (%)	xxx/xxx (%)	xxx/xxx (%)
Diagnosis – n/total no. (%)		
STEMI	xxx/xxx (%)	xxx/xxx (%)
NSTEMI	xxx/xxx (%)	xxx/xxx (%)
Unstable angina	xxx/xxx (%)	xxx/xxx (%)
Previous use of chronic statin therapy (6 months before randomization) n (%)	xxx/xxx (%)	xxx/xxx (%)
Medical history– n/total no. (%)		
Hypertension	xxx/xxx (%)	xxx/xxx (%)
Hypercholesterolemia	xxx/xxx (%)	xxx/xxx (%)
Diabetes mellitus	xxx/xxx (%)	xxx/xxx (%)
Tobacco use	xxx/xxx (%)	xxx/xxx (%)
Previous MI	xxx/xxx (%)	xxx/xxx (%)
Previous CABG	xxx/xxx (%)	xxx/xxx (%)
Previous Stroke	xxx/xxx (%)	xxx/xxx (%)
Renal Impairment	xxx/xxx (%)	xxx/xxx (%)
Obesity	xxx/xxx (%)	xxx/xxx (%)
Other medical therapy – n/total no. (%)		
Aspirin	xxx/xxx (%)	xxx/xxx (%)
Clopidogrel/Ticagrelor/Prasugrel	xxx/xxx (%)	xxx/xxx (%)
Beta-blockers	xxx/xxx (%)	xxx/xxx (%)
ACE inhibitors or ARA	xxx/xxx (%)	xxx/xxx (%)
Treatment strategy – n/total no. (%)		
PCI	xxx/xxx (%)	xxx/xxx (%)
CABG	xxx/xxx (%)	xxx/xxx (%)

Medical Management	xxx/xxx (%)	xxx/xxx (%)
Time hospital admission to PCI (hours) – mean ± sd	xx.x ± xx.x	xx.x ± xx.x
Time randomization to PCI (hours) – mean ± sd	xx.x ± xx.x	xx.x ± xx.x
Reason why did not performed PCI		
Clinical treatment	xxx/xxx (%)	xxx/xxx (%)
CABG	xxx/xxx (%)	xxx/xxx (%)
Final diagnosis is not ACS	xxx/xxx (%)	xxx/xxx (%)
Unknown	xxx/xxx (%)	xxx/xxx (%)

*STEMI denotes ST elevation myocardial infarction, Non-STEMI denotes Non ST elevation myocardial, infarction, MI denotes Myocardial Infarction, ACE denotes Angiotensin Converting Enzyme, ARA denotes Angiotensin II receptor Antagonist, PCI denotes Percutaneous Coronary Intervention, CABG denotes Coronary Artery Bypass Graft,

244 **Table 2:** Procedural Characteristics in Atorvastatin and Placebo

Procedural Characteristics	Atorvastatin (n = xxxx)	Placebo (n = xxxx)
Study-drug administration - n/total no. (%)	xxx/xxx (%)	xxx/xxx (%)
Didn't received study drug	xxx/xxx (%)	xxx/xxx (%)
More than 12h before PCI	xxx/xxx (%)	xxx/xxx (%)
2h to 12h before PCI	xxx/xxx (%)	xxx/xxx (%)
Until 2h before PCI	xxx/xxx (%)	xxx/xxx (%)
Until 2h after PCI	xxx/xxx (%)	xxx/xxx (%)
2h to 4h after PCI	xxx/xxx (%)	xxx/xxx (%)
Received reload dose	xxx/xxx (%)	xxx/xxx (%)
Heparin used to support PCI - n/total no. (%)	xxx/xxx (%)	xxx/xxx (%)
Stent - n/total no. (%)	xxx/xxx (%)	xxx/xxx (%)
Bare-metal stent only	xxx/xxx (%)	xxx/xxx (%)
≥1 Drug-eluting stent	xxx/xxx (%)	xxx/xxx (%)
Restenotic lesions - n/total no. (%)	xxx/xxx (%)	xxx/xxx (%)
Multivessel PCI- n/total no. (%)	xxx/xxx (%)	xxx/xxx (%)
Intravascular Ultrasound Use - n/total no. (%)	xxx/xxx (%)	xxx/xxx (%)
Ballon post-dilatation - n/total no. (%)	xxx/xxx (%)	xxx/xxx (%)
Stent deployment pressure (atm) - mean ± sd	xx.x ± xx.x	xx.x ± xx.x
No. of stents per patient - mean ± sd	xx.x ± xx.x	xx.x ± xx.x
TIMI Flow Pre-procedural 3 - n/total no. (%)	xxx/xxx (%)	xxx/xxx (%)
TIMI Flow Post-procedural 3 - n/total no. (%)	xxx/xxx (%)	xxx/xxx (%)
Procedural complications - n/total no. (%)	xxx/xxx (%)	xxx/xxx (%)
Coronary Dissection	xxx/xxx (%)	xxx/xxx (%)
Acute Coronary Artery Occlusion during PCI	xxx/xxx (%)	xxx/xxx (%)
Coronary Slow-Flow Phenomenon	xxx/xxx (%)	xxx/xxx (%)
Severe Side-Branch Stenosis	xxx/xxx (%)	xxx/xxx (%)
Side-Branch Closure	xxx/xxx (%)	xxx/xxx (%)
Acute Coronary Perforation during PCI	xxx/xxx (%)	xxx/xxx (%)
Coronary Occlusion after PCI	xxx/xxx (%)	xxx/xxx (%)

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249 **Table 3:** Laboratory Assays in Atorvastatin and Placebo

Laboratory Assays	Atorvastatin (n = xxxx)	Placebo (n = xxxx)	P Value
Prior PCI			
Total Cholesterol – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
LDL Cholesterol – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
HDL Cholesterol – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
Triglycerides – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
Serum Creatinine Levels – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
Alanine Transaminase (ALT) – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
Aspartate Transaminase (AST) – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
Creatine Phosphokinase (CPK) – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
Aftet PCI			
Total Cholesterol – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
LDL Cholesterol – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
HDL Cholesterol – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
Triglycerides – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
Serum Creatinine Levels – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
Alanine Transaminase (ALT) – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
Aspartate Transaminase (AST) – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx
Creatine Phosphokinase (CPK) – mean ± sd	xx.x ± xx.x	xx.x ± xx.x	x.xx

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252 **Table 4:** Primary and Secondary Outcomes

Outcomes	Atorvastatin	Placebo	Hazard ratio (95% CI*)	P Value
Primary Outcome				
MACE at 30 days	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Secondary Outcomes				
Death	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Cardiovascular Death	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Myocardial Infarction	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Peri-PCI MI	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Others	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Coronary Revascularization	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Urgent/Target Vessel	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Stroke	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Stent Thrombosis	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Secondary Outcomes at 7 days or hospital discharge				
Bleeding†	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx) †	xx.xx
Rhabdomyolysis†	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx) †	xx.xx
PCI only population				
Primary Outcome				
MACE at 30 days	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Secondary Outcomes				
Death	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Cardiovascular Death	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Myocardial Infarction	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Peri-PCI MI	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Others	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Coronary Revascularization	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Urgent/Target Vessel	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Stroke	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Stent Thrombosis	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	xx.xx
Secondary Outcomes at 7 days or hospital discharge				
Bleeding†	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx) †	xx.xx

* CI denotes confidence interval.

† Effect estimates are risk ratios.

Table 5: Subgroup Analyses of the Primary Outcome

Subgroups	Atorvastatin	Placebo	Hazard ratio (95% CI*)	P value for interaction
Sex				
Male	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	x.xx
Female	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	
Age				x.xx
≤ 65 yr	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	
>65	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	
Diagnosis				
STEMI	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	x.xx
NSTEMI	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	
UA	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	
Previous use of statin				
No	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	x.xx
Yes	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	
Stents				
DES	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	x.xx
BMS	xxx/xxx (%)	xxx/xxx (%)	x.xx (x.xx-x.xx)	

* CI denotes confidence interval, STEMI denotes ST elevation myocardial infarction, NSTEMI denotes Non-ST elevation myocardial infarction, UA denotes unstable angina, DES denotes drug eluting stent, BMS denotes bare metal stent

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